USES OF DPP-IV INHIBITORS

This application claims priority of EP 06 009 203, which is hereby incorporated by reference in its entirety.

BACKGROUND OF THE INVENTION

1. Field of the Invention

The specification describes the use of selected DPP IV inhibitors for the treatment of physiological functional disorders and for reducing the risk of the occurrence of such functional disorders in at-risk patient groups. In addition, the use of the above-mentioned DPP IV inhibitors in conjunction with other active substances is described, by means of which improved treatment outcomes can be achieved. These applications may be used to prepare corresponding medicaments.

2. Description of the Prior Art

The enzyme DPP-IV, also known by the name CD26, is a serine protease which promotes the cleaving of dipeptides in proteins with a proline or alanine group at the N-terminal end. DPP-IV inhibitors thereby influence the plasma level of bioactive peptides including the peptide GLP-1 and are highly promising molecules for the treatment of diabetes mellitus.

Type 1 diabetes mellitus, which occurs mainly in juveniles under 30 years of age, is categorised as an autoimmune disease. With a corresponding genetic disposition and under the influence of various factors, insulitis occurs, followed by destruction of the B-cells, so that the pancreas is no longer able to produce much, if any, insulin.

Type 2 diabetes mellitus is not categorised as an autoimmune disease and manifests itself in a fasting blood sugar level exceeding 125 mg of glucose per dl of plasma; the measurement of blood glucose values is a standard procedure in routine medical analysis. Prediabetes is suspected if the fasting blood sugar level exceeds the maximum normal level of 99 mg of glucose per dl of plasma but does not exceed the threshold of 125 mg of glucose per dl of plasma, which is relevant for diabetes. This is also referred to as pathological fasting glucose (impaired fasting glucose). Another indication of prediabetes is a disrupted glucose tolerance, i.e. a blood sugar level of 140-199 mg of glucose per dl of plasma 2 hours after taking 75 mg of glucose on an empty stomach within the scope of an oral glucose tolerance test.

If a glucose tolerance test is carried out, the blood sugar level of a diabetic will be in excess of 199 mg of glucose per dl of plasma 2 hours after 75 g of glucose have been taken on an empty stomach. In a glucose tolerance test 75 g of glucose are administered orally to the patient being tested after 10-12 hours of fasting and the blood sugar level is recorded immediately before taking the glucose and 1 and 2 hours after taking it. In a healthy subject the blood sugar level will be between 60 and 99 mg per dl of plasma before taking the glucose, less than 200 mg per dl 1 hour after taking it and less than 140 mg per dl after 2 hours. If after 2 hours the value is between 140 and 199 mg this is regarded as abnormal glucose tolerance or in some cases glucose intolerance.

In the monitoring of the treatment of diabetes mellitus the HbA1c value, the product of a non-enzymatic glycation of the haemoglobin B chain, is of exceptional importance. As its formation depends essentially on the blood sugar level and the life time of the erythrocytes the HbA1c in the sense of a "blood sugar memory" reflects the average blood sugar level of the preceding 4-12 weeks. Diabetic patients whose HbA1c level has been well controlled over a long time by more intensive diabetes treatment (i.e. <6.5% of the total haemoglobin in the sample) are significantly better protected from diabetic microangiopathy. The available treatments for diabetes can give the diabetic an average improvement in their HbA1c level of the order of 1.0-1.5%. This reduction in the HbA1C level is not sufficient in all diabetics to bring them into the desired target range of <6.5% and preferably <6% HbA1c.

If insulin resistance can be detected this is a particularly strong indication of the presence of the complex metabolic disorder of prediabetes. Thus, it may be that in order to maintain glucose homoeostasis a person needs 2-3 times as much insulin as another person. The most certain method of determining insulin resistance is the euglycaemic-hyperinsulinaemic clamp test. The ratio of insulin to glucose is determined within the scope of a combined insulin-glucose infusion technique. There is found to be insulin resistance if the glucose absorption is below the 25th percentile of the background population investigated (WHO definition). Rather less laborious than the clamp test are so called minimal models in which, during an intravenous glucose tolerance test, the insulin and glucose concentrations in the blood are measured at fixed time intervals and from these the insulin resistance is calculated. Another method of measurement is the mathematical HOMA model. The insulin resistance is calculated by means of the fasting plasma glucose and the fasting insulin concentration. In this method it is not possible to distinguish between hepatic and peripheral insulin resistance. These processes are not really suitable for evaluating insulin resistance in daily practice. As a rule, other parameters are used in everyday clinical practice to assess insulin resistance. Preferably, the patient's triglyceride concentration is used, for example, as increased triglyceride levels correlate significantly with the presence of insulin resistance.

To simply somewhat, in practice it is assumed that people are insulin-resistant if they have at least 2 of the following characteristics:

1) overweight or obesity
2) high blood pressure
3) dyslipidaemia (an altered content of total lipids in the blood)
4) at least one close relative in whom abnormal glucose tolerance or type 2 diabetes has been diagnosed.

Overweight means in this instance that the Body Mass Index (BMI) is between 25 and 30 kg/m^2, the BMI being the quotient of the body weight in kg and the square of the height in meters. In manifest obesity the BMI is 30 kg/m^2 or more.

It is immediately apparent, from the above definition of insulin resistance, that hypotensive agents are suitable and indicated for treating it if, among other things, high blood pressure is found in the patient.

A similar indication of prediabetes is if the conditions for metabolic syndrome are met, the main feature of which is insulin resistance. According to the ATP IHINCEP Guidelines (Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) in the Journal of the American Medical Association 285:2486-2497, 2001) metabolic syndrome is present if a patient has at least 3 of the following characteristics:

1) Abdominal obesity, defined as a waist measurement of >40 inches or 102 cm in men and >35 inches or 94 cm in women
2) Triglyceride levels>150 mg/dl
3) HDL-cholesterol levels<40 mg/dl in men
4) High blood pressure>130/>85 mm Hg
5) Fasting blood sugar of >110 mg/dl

This definition of metabolic syndrome immediately shows that hypotensives are suitable for treating it if the patient is found to have high blood pressure, among other things.

A triglyceride blood level of more than 150 mg/dl also indicates the presence of pre-diabetes. This suspicion is con-